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EXAMINER

LU, FRANK WEI MIN

ART UNIT	PAPER NUMBER
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1634

DATE MAILED: 01/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/627,950	Applicant(s) RADTKEY ET AL.	
	Examiner Frank W. Lu	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.138(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 November 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
4a) Of the above claim(s) 10-14 and 21 is/are withdrawn from consideration.
5) ☐ Claim(s) _____ is/are allowed.
6) ☒ Claim(s) 1-9, 15-20 and 22-40 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
10) ☒ The drawing(s) filed on 24 July 2003 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>2/04 and 5/04</u> . | 6) <input type="checkbox"/> Other: <u>Initials</u> |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-40 and specie (1) (claim 9) and species (7) (claim 20) in the reply filed on November 7, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, claims 1-9, 15-20, and 22-40 will be examined.

Information Disclosure Statement

2. The information disclosure statement filed on February 17, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document and each non-patent literature publication. Although applicant states that "copies of some or all of the references listed on the attached Form PTO/SB/08A are not enclosed herewith because they were previously cited by or submitted to the Patent and Trademark Office in prior copending or related applications for which a claim for priority under 35 U.S.C. §120 has been made in the instant application" (see page 2 of INFORMATION DISCLOSURE STATEMENT filed on February 17, 2004), applicant does not indicate which copending or related applications have these cited foreign patent documents and non-patent literature publications. Therefore, the cited foreign patent documents and non-patent literature publications listing in IDS filed on February 17, 2004 have not been considered in this office action.

Drawings

3. Some of words in Figures 2-7 and 9 are hard to read. New corrected drawings are required in this application in the response to this office action.

Sequence Rules Compliance

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Direct the reply to the undersigned.

Specification

5. The disclosure is objected to because of the following informalities: (1) there are many nucleotide sequences with more than 10 nucleotides in Tables 5, 6, 8, 11, and 12 (see the specification, pages 50, 53, and 67-70). However, there are no SEQ ID Nos for these nucleotide sequences in pages 50, 53, and 67-70 of the specification; and (2) some words in Tables 7 and 12 (see pages 52 and 70 of the specification) are between two columns and are hard to read.

Appropriate correction is required.

Claim Objections

6. Claim 1 is objected to because of the following informalities: (1) “patient sample nucleic acid” in line 3 should be “patient sample nucleic acids” or “a patient sample nucleic acid”; and (2) “hyubridization” in last line should be “hybridization”.
7. Claims 3-5 are objected to because of the following informality: “A method” should be “The method”.
8. Claim 40 is objected to because of the following informality: “the sample of patient nucleic acid” should be “the samples of patient nucleic acid”.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Scope of Enablement

Claims 1 and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using the method recited in claim 1 for detecting a hybridization event between at least one discrimination and samples of patient nucleic acid, does not reasonably provide enablement for using the method recited in claim 1 for detecting a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court considered the issue of enablement in molecular biology. The Court summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Court also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

To begin, there is no direction or guidance in the specification to show that the method recited in claim 1 can be used for detecting a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy. While the relative skill in the art is very high (the Ph.D. degree with laboratory experience), there is no predictability whether the method recited in claim 1 can be used for detecting a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy.

Claim 1 is directed to a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid. Claims 24-26 further limit that the loci in claim 1 is a loci of a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy. Since the one or more blockers and the at least one discriminator recited in claim 1 are not specific for a genetic disease

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such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy, in view of claims 24-26, it is unclear how the one or more blockers and the at least one discriminator recited in claim 1 which are non-specific for a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy can be used for detecting a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy.

With above unpredictable factor, the skilled artisan will have no way to predict the experimental results. Accordingly, it is concluded that undue experimentation is required to make the invention as it is claimed. The undue experimentation at least includes to test whether the method recited in claim 1 can be used for detecting a genetic disease such as cystic fibrosis, Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-9, 15-20, and 22-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1, 28, 34, and 40 are rejected as vague and indefinite. Although claim 1 or 28 or 34 or 40 is directed to a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid, there is no method step for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid in the

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of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid in the content of claim 1 or 28 or 34 or 40 and the goal of the claims (see preamble of the claims) can not be reached. Please clarify.

14. Claim 15 is rejected as vague and indefinite. Since claim 1 does not limit samples of patient nucleic acid to genomic nucleic acid containing the known polymorphisms, it is unclear how multiple amplifications are accomplished in multiplex polymerase-based reactions with specially selected primers for identified loci of genomic nucleic acid containing the known polymorphisms. Please clarify.

15. Claim 23 is rejected as vague and indefinite. Since there is no word "color" in claim 1, it is unclear how amplification controls can be indicated by different colors. Please clarify.

16. Claim 28 is rejected as vague and indefinite because it is unclear that "probes" in last line of the claim are identical to at least two probes in line 4 of the claim or not and it is unclear that "patient sample" in last line of the claim are identical to a patient sample in line 3 or not. Please clarify.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 1-9, 15, 17-20, 22-24, and 26-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Nerenberg *et al.*, (US Patent No. 6,468,742 B2, filed on April 12, 1999).

Regarding claim 1, Nerenberg *et al.*, teach a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid, comprising the steps of: providing patient sample nucleic acids containing multiple loci (ie., the single stranded target nucleic acids of interest) at a site (ie., the electronically addressable microchip); providing one or more blockers (ie., the at least one stabilizer oligonucleotide), the blockers being selected for particular loci; hybridizing the blockers with the patient sample nucleic acid, leaving at least one loci unblocked; providing at least one discriminator (ie., the at least one reporter oligonucleotide), the discriminator being capable of binding with the at least one unblocked loci; hybridizing the discriminators with the patient sample; and detecting the formation of a hybridization event (see abstract, columns 5-9, claims 1-125 in columns 27-38, and Figures 2 and 4).

Regarding claims 2-6 and 22, since Nerenberg *et al.*, teach that the capture sites in column 1 and 2 of the microchip receive a Hemochromatosis wild type and Factor V mutant while the sites in column 4 and 5 of the microchip are targeted with both Hemochromatosis and Factor V Heterozygotes, reporting is done sequentially, first with the allele-specific Hemochromatosis reporters (SEQ ID Nos. 11 and 12) and then the allele-specific Factor V reporters (SEQ ID Nos. 16 (CGCCTGTCCAG-CR6G) and 17 (TGCCTGTCCAG-Far Red), and before Factor V reporters are passively hybridized, all remaining Hemochromatosis reporters are stripped from the microarray (see column 12, lines 14-45, column 20, lines 1-30, and claims 1, 16, and 17 in columns 27-29), Nerenberg *et al.*, disclose the step of providing a second blocker

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set (ie., the allele-specific Factor V reporters) after performing the detecting step (ie., detecting using the allele-specific Hemochromatosis reporters) as recited in claim 2, wherein the blockers are changed sequentially at a single site (ie., first allele-specific Hemochromatosis reporters and then the allele-specific Factor V reporters in the site of column 1 or 2) as recited in claim 4, different blockers (ie., allele-specific Hemochromatosis reporters and the allele-specific Factor V reporters) are provided to different sites (ie., the sites of columns 1, 2, 4, and 5) as recited in claim 5, the site comprises a site of an actively addressable electronic microarray as recited in claim 6, and the multiple patient samples (ie., Hemochromatosis wild type, Factor V mutant, and Hemochromatosis and Factor V Heterozygotes) are provided on multiple sites (ie., columns 1, 2, 4, and 5) of the microarray as recited in claim 22.

Regarding claim 3, since Nerenberg *et al.*, teach to contact the target nucleic acid of the interest representing one or both wild type and mutant alleles with both wild type and mutant reporter oligonucleotides (see column 16 and Figure 2), Nerenberg *et al.*, disclose that the identity (ie., without or with a mutant base) of the loci involved in the hybridization event is determined by selectively blocking the previously unblocked loci (ie., a region that hybridizes to both wild type and mutant reporter oligonucleotides but does not hybridize to the at least one stabilizer oligonucleotide) as recited in claim 3.

Regarding claim 7, Nerenberg *et al.*, teach that the addressable electronic microarray includes a permeation layer (see column 12, lines 49-67, column 13, lines 1-3, and Figures 1A and 1B).

Regarding claims 8 and 9, Nerenberg *et al.*, teach that the patient sample is amplified as recited in claim 8 wherein the amplification includes polymerase chain reaction (PCR) as recited in claim 9 (see claims 1 and 22-29 in columns 27-30).

Regarding claim 15, Nerenberg *et al.*, teach that multiple amplifications are accomplished in multiplex polymerase-based reactions with specially selected primers for identified loci of genomic nucleic acid containing the known polymorphisms (see column 12, lines 14-45, column 20, lines 1-30 and Figure 12).

Regarding claim 17, Nerenberg *et al.*, teach that at least two loci (ie., the sites that two reporter probes 43 and 44 hybridize to) are unblocked (see column 21, lines 53-62 and Figures 4a and 4b).

Regarding claim 18, Nerenberg *et al.*, teach performing a screening step (ie., analyzing unknown hemochromatosis samples) (see column 19, lines 38-65).

Regarding claims 19 and 20, Nerenberg *et al.*, teach that the patient sample nucleic acid comprises multiple segments containing different loci (ie., the sites that two reporter probes 43 and 44 hybridize to) as recited in claim 19 wherein the multiple segments containing different loci are affixed to the same site (ie., the site on the microchip) as recited in claim 20 (see column 21, lines 53-62 and Figures 4a and 4b).

Regarding claim 23, Nerenberg *et al.*, teach that amplification controls (ie., the wild type reporter is a control of mutant reporter) indicated by different colors (see columns 17 and 18).

Regarding claim 24, Nerenberg *et al.*, teach that the loci are indicative of genetic diseases (see column 6, lines 43-46 and column 13, lines 36-49).

Regarding claim 26, Nerenberg *et al.*, teach that the genetic disease is selected from the group consisting of Beta-Thalassemia, hereditary hemochromatosis, Gaucher, Tay-sachs, Nieman-Pick, HIV, and epilepsy (see column 12, lines 14-45).

Regarding claim 27, , Nerenberg *et al.*, teach including a stabilizer adjacent the discriminator (ie., the probe 44) (see Figure 4a).

Regarding claims 28 and 31, Nerenberg *et al.*, teach including a stabilizer adjacent the discriminator (ie., the reporter probe 44) (see Figure 4A and column 21, lines 53-62).

Regarding claim 28, since Nerenberg *et al.*, teach that the amplification products containing Hemochromatosis wild type, Factor V mutant and Hemochromatosis and Factor V Heterozygotes are combined together along with each of their 30-mer stabilizer oligos, the capture site in column 1 and 2 of the microchip receive a Hemochromatosis wild type and Factor V mutant while the sites in column 4 and 5 of the microchip are targeted with both Hemochromatosis and Factor V Heterozygotes, reporting is done sequentially, first with the allele-specific Hemochromatosis reporters (SEQ ID Nos. 11 and 12) and then the allele-specific Factor V reporters (SEQ ID Nos. 16 (CGCCTGTCCAG-CR6G) and 17 (TGCCTGTCCAG-Far Red), and before Factor V reporters are passively hybridized, all remaining Hemochromatosis reporters are stripped from the microarray (see column 12, lines 14-45, column 20, lines 1-30, and claims 1, 16, and 17 in columns 27-29), Nerenberg *et al.*, disclose a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid comprising the steps of: providing a patient sample containing multiple loci, performing a screening step, comprising providing at least two probes for different loci (ie., the stabilizer oligo for Hemochromatosis and the allele-specific Hemochromatosis reporters), and detecting the

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presence of a hybridization event between the patient sample and the probes, and, if a hybridization event is detected, providing a first set of blockers to the loci (ie., the stabilizer oligo for Factor V), the set of blockers comprising a subset of the sites corresponding to the probes, and providing probes (ie., the allele-specific Factor V reporters) to a patient sample, and detecting a hybridization event as recited in claim 28 wherein the screening step is performed at one site (ie., the site in column 1), and if a hybridization event is detected, multiple sites containing the patient samples (ie., columns 2 and 5) are subsequently probed as recited in claim 31.

Regarding claims 29 and 30, Nerenberg *et al.*, teach that, in the screening step there are at least three probes for different loci as recited in claim 29 and there are at least five probes for different loci (see Figures 4a and 6a).

Regarding claims 32 and 33, Nerenberg *et al.*, teach that different blocker sets (ie., the stabilizer oligo for Hemochromatosis and the stabilizer oligo for Factor V) are provided to the different patient samples at the multiple sites (ie., the sites of columns 1, 2, 4, and 5) as recited in claim 32. Since Nerenberg *et al.*, teach that the amplification products containing Factor V mutant and Hemochromatosis and Factor V Heterozygotes only have a single polymorphism (see column 12, lines 14-45), Nerenberg *et al.*, disclose that the blocker sets (ie., the stabilizer oligo for Hemochromatosis or the stabilizer oligo for Factor V) block all but one loci (ie., single polymorphism site for Hemochromatosis or Factor V) as recited in claim 33.

Regarding claim 34, since Nerenberg *et al.*, teach that step (b) occurs before step (c) (see claims 1 and 4 in columns 27 and 28), Nerenberg *et al.*, disclose a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid

comprising the steps of: loading (ie., electronically addressing) a patient sample containing multiple loci (ie., the single stranded target nucleic acids of interest) at multiple sites (ie., the multiple sites in the microchip), including at least a first site and a second site, and providing a first set of blockers (ie., multiple copies of wild type reporter oligonucleotide) selectively for a subset of the loci to the first site (ie., one of probe 90 attached sites in Figure 3) and a second set of blockers (ie., multiple copies of mutant reporter oligonucleotide), which are different from the first set of blockers, selectively to a different subset of the loci at the second site (ie., another probe 90 attached sites in Figure 3) (see abstract, columns 5-9 and 21 , claims 1-125 in columns 27-38, and Figures 3 and 4a).

Regarding claims 35 and 36, Nerenberg *et al.*, teach that there exist unblocked loci (ie., the sites adjacent to probe 44) as recited in claim 35 and discriminators (ie., probe 43) are provided for detecting the unblocked loci (see Figure 4a)

Regarding claim 37, Nerenberg *et al.*, teach that the multiple sites comprise sites of an actively addressable electronic microarray (see claim 1 in columns 27 and 28 and Figures 1A and 1B).

Regarding claim 38, Nerenberg *et al.*, teach that the addressable electronic microarray includes a permeation layer (see column 12, lines 49-67, column 13, lines 1-3, and Figures 1A and 1B).

Regarding claim 39, Nerenberg *et al.*, teach that the patient sample is amplified (see claims 1 and 22-29 in columns 27-30).

Regarding claim 40, Nerenberg *et al.*, teach a method for detecting members of a set of polymorphisms that occur at identified loci in samples of patient nucleic acid, comprising the

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steps of: attaching the samples of patient nucleic acid to a test site (ie., the electronically addressable microchip), the patient sample having multiple identified loci (ie., the single stranded target nucleic acids of interest); providing a blocker set (ie., the at least one stabilizer oligonucleotide) to the patient sample so as to block some, but not all, of the loci; and providing discriminators (ie., the at least one reporter oligonucleotide) for detecting unblocked loci (see abstract, columns 5-9 and 16 , claims 1-125 in columns 27-38, and Figures 2 and 4).

Therefore, Nerenberg *et al.*, teach all limitations recited in claims 1-9, 15, 17-20, 22-24, and 26-40.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg *et al.*, as applied to claims 1-9, 15, 17-20, 22-24, and 26-40 above, and further in view of Arnold *et al.*, (US Patent NO. 6,410,231, filed on February 26, 1999).

The teachings of Nerenberg *et al.*, have been summarized previously, *supra*.

Nerenberg *et al.*, do not disclose that the discriminator hybridizes with a universal reporter as recited in claim 16.

Arnold *et al.*, that a sandwich hybridization using an universal probe. Since “wherein” phase in claim 16 is not considered as a method step, the universal probe taught by Arnold *et al.*,

is considered as a complex formed by the discriminator (ie., the part of the probe which hybridizes to the target nucleic acid) hybridized with a universal reporter (ie., the part of the probe having sequence NNTNN) (see Figure 3).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 16 wherein the discriminator hybridizes with a universal reporter in view of the patents of Nerenberg *et al.*, and Arnold *et al.*. One having ordinary skill in the art would have been motivated to do so because Arnold *et al.*, has successfully used an universal probe for the sandwich hybridization and the simple replacement of one kind of probe (ie., the discriminator taught by Nerenberg *et al.*,) from another kind of probe (i.e., the universal probe taught by Arnold *et al.*,) during the process for performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the probe taught by Nerenberg *et al.*, and the universal probe taught by Arnold *et al.*, are used for the same purpose (ie., hybridizing to unblocked loci).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

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21. Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nerenberg *et al.*, as applied to claims 1-9, 15, 17-20, 22-24, and 26-40 above, and further in view of Song *et al.*, (US Patent NO. 6451,526, filed on January 15, 1999).

The teachings of Nerenberg *et al.*, have been summarized previously, *supra*.

Nerenberg *et al.*, do not disclose that the genetic disease is cystic fibrosis as recited in claim 25.

Song *et al.*, suggest that different target nucleic acids including ApoE4, cystic fibrosis, Factor V, and HFE (hemochromatosis) genes as well as oncogenes such as the RET proto-oncogene can be used for mutation detection (see column 5, last paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 25 wherein the genetic disease is cystic fibrosis in view of the patents of Nerenberg *et al.*, and Song *et al.*. One having ordinary skill in the art would have been motivated to do so because and Song *et al.*, suggest that different target nucleic acids including ApoE4, cystic fibrosis, Factor V, and HFE (hemochromatosis) genes as well as oncogenes such as the RET proto-oncogene are used for mutation detection (see column 5, last paragraph) and the simple replacement of one kind of target nucleic acid (ie., the target nucleic acid taught by Nerenberg *et al.*,) from another kind of target nucleic acid (i.e., the target nucleic acid containing cystic fibrosis gene taught by Song *et al.*,) during the process for performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because Nerenberg *et al.*, suggest their method is

used for the accurate detection of diseased states, especially clonal tumor disease states, neurological disorders and predisposition to genetic disease (see column 9, lines 43-46).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. In re Rose 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

Conclusion

22. No claim is allowed.

23. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (571)272-0745.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

A handwritten signature in black ink, appearing to read "Frank Lu", is positioned above the typed name.

Frank Lu
Primary Examiner
January 20, 2006

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☐ 7. Other: _____

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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